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HOWARD, ZACHARY C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,195	PEPICELLI ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 25-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 25-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,3,4 and 25-31* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 7/7/08 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 7/7/08 has been entered in full. Claims 1 and 27 are amended. Claims 2 and 5-24 were previously canceled. New claims 29-31 are added.

Claims 1, 3, 4 and 25-31 are under consideration in the instant application.

Information Disclosure Statement

The Information Disclosure Statement of 7/7/08 has been considered.

Withdrawn Objections and/or Rejections

The following refers to the Advisory Action mailed 5/12/08.

The rejection of claims 27 and 28 under 35 U.S.C. § 112, first paragraph at pg 2 for containing new matter is *withdrawn* in view of Applicants' amendments to the claims.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 4, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marigo et al (U.S. Patent No. 6,261,786, published 7/17/01, filed 7/2/96 and claiming priority to 12/30/93; cited previously) in view of Fujita et al (9/18/1997, Biochemical and Biophysical Research Communications, 238: 658-665; cited previously). This rejection was set forth previously and maintained at pg 2 of the 5/12/08 Advisory Action.

The basis of the rejection is first restated in view of Applicants' amendments to the claims to specifically recite two discrete method steps, and then Applicants arguments are addressed.

The recitation of "screening for an agent for inhibiting or reducing the proliferation or growth of lung cancer cells" in the preamble of claim 1 is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Therefore, claim 1 encompasses a method comprising contacting lung cancer cells with an agent that is a small organic molecule, and determining (1) whether the agent inhibits, as compared to a control hedgehog/patched signal transduction as compared to a control and (2) whether the agent inhibits cell proliferation or growth as compared to a control.

Marigo teaches "cell-based assays for identifying small molecule agonists/antagonists" (col 51, lines 24-25) and that the test compound can be a "small organic molecule" (column 10, line 60). Marigo teaches that "cells which are sensitive to hedgehog induction, e.g. patched-expressing cells, can be contacted with a hedgehog protein and a test agent of interest, with the assay scoring for anything from simple binding to the cell to modulation in hedgehog inductive responses by the target cell in the presence and absence of the test agent. As with the cell-free assays, agents which produce a statistically significant change in hedgehog activities (either inhibition or potentiation) can be identified" (col 51, lines 27-35). Marigo further teaches that patched gene expression is responsive to Shh signaling. Marigo further teaches that "[a]fter identifying certain test compounds as potential modulators of the target hedgehog receptor activity, the practitioner of the subject assay will continue to test the efficacy and specificity of the selected compound both in vitro and in vivo ... for subsequent in

vivo testing … agents identified in the subject assay can be formulated in pharmaceutical preparations for in vivo administration to an animal, preferably a human". Marigo further teaches that, "the present invention facilitates the development of assays which can be used to screen for drugs, including hedgehog homologs, which are either agonists or antagonists of the normal cellular function of the subject hedgehog polypeptides, or of their role in the pathogenesis of cellular differentiation and/or proliferation and disorders related thereto" (col 48, lines 40-46).

Marigo does not teach a method of screening using lung cancer cells. Marigo does not teach a method of screening that specifically includes two method steps: (1) determining, as compared to a control, whether the agent inhibits or attenuates hedgehog signaling and (2) determining, as compared to a control, whether the agent inhibits cell proliferation or growth.

Fujita teaches "Shh-N stimulated the cell growth of LK-2 cells, while anti-Shh-N inhibited the cell growth of LK-2 cells (Figure 5). Thus Shh of LK-2 cells seem to stimulate their own cell growth through interaction with PTC by an autocrine mechanism. LK-2 cells are useful for the study on the Shh-PTC signal involved in the cell proliferation" (pg 663). In Figure 5C, the inhibition of growth of the LK-2 cells in the presence of the anti-Shh-N antibody is shown as compared to a control (normal rat immunoglobulin). The growth assays were performed in cell culture and the Shh-N or anti-Shh-N was added to the culture medium (see Materials and Methods on pg 659-660). LK-2 is a human lung squamous carcinoma cell line (see Abstract). Fujita further describes detection of patched gene expression in the LK-2 cells (pg 660). Fujita further teaches that "Shh was also positive in the three lung squamous carcinoma tissues…while Shh was negative the epithelium of normal lung tissue of the same patients" (pg 661).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to contact a culture of the LK-2 lung cancer cells taught by Fujita with a small organic molecule as taught by Marigo and to measure hedgehog signaling pathway (by measuring patched gene expression) as compared to a control as taught by Marigo (i.e., in the presence and absence of the test compound) and to further

measure growth as compared as taught by Fujita as compared to a control (i.e., the presence and absence of a test compound). Marigo provides motivation to identify hedgehog signaling antagonists that are also antagonists of cellular proliferation by teaching, "the present invention facilitates the development of assays which can be used to screen for drugs, including hedgehog homologs, which are either agonists or antagonists of the normal cellular function of the subject hedgehog polypeptides, or of their role in the pathogenesis of cellular differentiation and/or proliferation and disorders related thereto" (col 48, lines 40-46). Thus, the person of ordinary skill in the art would have been motivated to screen to first identify a small organic molecule that is an antagonist (inhibitor) of hedgehog signaling and then screen to determine if it is also an inhibitor of lung cancer cell growth.

The method that is obvious over Marigo in view of Fujita meets the limitations of claims 1, 3, 25 and 26. It is noted that the LK-2 lung squamous cell carcinoma cells meet the additional limitations presented in claims 25 and 26 because squamous cell carcinoma is a form of non-small cell lung cancer (claim 25) and is both a lung cell carcinoma and a squamous cell carcinoma (claim 26).

It would have further been obvious to the person of ordinary skill in the art at the time the invention was made to further modify the method of Marigo in view of Fujita described above to perform an in vivo method of screening comprising contacting the lung squamous carcinoma cells in a patient taught by Fujita with a small organic molecule that is administered as a composition as taught by Marigo. The person of ordinary skill in the art would have been motivated to do so in order to identify a small organic molecule that is an antagonist (inhibitor) of hedgehog signaling and also an antagonist of lung squamous cancer cell growth in a patient.

Applicants' arguments (7/7/08; pg 4-6) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicants first argue that "reliance on inherency in an attempt to overcome deficiencies in the teachings of the cited references is inappropriate" (pg 5).

Applicants' arguments have been fully considered but are not found persuasive. In view of Applicants' amendments to the claims, the rejection has been restated. No reliance on inherency is included in the restated rejection.

Applicants next argue that the claimed method has been amended to clarify that the "claimed method is directed to screening assays in which two parameters are evaluated" (pg 5). Applicants refer to arguments detailed in the after final response "why the cited references fail to render the claimed invention obvious" (pg 5). In the 3/3/08 response, Applicants argued that Marigo et al and Fujita et al, either individually or in combination, fail to "teach or suggest assays in which screening is based on evaluating multiple parameters"; that "neither reference teaches the use of multiple parameters, and neither reference suggest the desirability of screening based on evaluating multiple parameters"; and that "the fact that each reference describes screens based on analysis of one parameter teaches away from methods based on analyzing multiple parameters, as there is no motivation to design a more involved assay" (pg 8). Applicants argue that the combined teachings of Marigo and Fujita fail to satisfy the criteria set forth in MPEP 2142 to establish a prima facie case of obviousness.

Applicants' arguments have been fully considered but are not found persuasive. The claimed method directed to screening assays in which two parameters are evaluated is obvious for the reasons set forth in the restated rejection above. It is true that Marigo and Fujita each teach different parameters for use in screening. However, the rejection under 103(a) is not based on the teachings of Fujita alone, but rather on the teachings of Marigo in view of the teachings of Fujita. Furthermore, Marigo provides motivation for the obviousness of a method including evaluation of each parameter. Specifically, Marigo teaches, "the present invention facilitates the development of assays which can be used to screen for drugs, including hedgehog homologs, which are either agonists or antagonists of the normal cellular function of the subject hedgehog polypeptides, or of their role in the pathogenesis of cellular differentiation and/or proliferation and disorders related thereto" (col 48, lines 40-46). Thus, Marigo teaches that the assays can be used to screen for drugs that are modulators of the role of hedgehog polypeptides in the pathogenesis of cellular proliferation. Thus, in view of the

teachings of Fujita it would be immediately obvious to combine the teachings of the two references to screen for molecules that inhibit the hedgehog pathway (as taught by Marigo) and to screen for those that inhibit cellular growth (as taught by Fujita). It is therefore maintained that the combined teachings of Marigo and Fujita satisfy the criteria set forth in MPEP 2142 to establish a *prima facie* case of obviousness.

New rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27 and 28 rejected under 35 U.S.C. 103(a) as being unpatentable over Marigo et al (U.S. Patent No. 6,261,786, published 7/17/01, filed 7/2/96 and claiming priority to 12/30/93; cited previously) in view of Bellusci (January 1997. Development. 124: 53-63; cited as reference CB on the 12/3/03 IDS) and further in view of Cardoso et al (1996. Developmental Dynamics. 207: 47-59).

The recitation of "screening for an agent for inhibiting or reducing the proliferation or growth of cells" in the preamble of claim 27 is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Therefore, claim 27 encompasses a method comprising contacting cultured non-cancerous lung cells with an agent, and determining, as compared to a control, whether the agent inhibits (1) hedgehog/patched signal transduction and (2) cell proliferation. Claim 28 depends from claim 27 and limits the agent to a small organic molecule.

Marigo teaches "cell-based assays for identifying small molecule agonists/antagonists" (col 51, lines 24-25) and that the test compound can be a "small organic molecule" (column 10, line 60). Marigo teaches that "cells which are sensitive to hedgehog induction, e.g. patched-expressing cells, can be contacted with a hedgehog protein and a test agent of interest, with the assay scoring for anything from simple

binding to the cell to modulation in hedgehog inductive responses by the target cell in the presence and absence of the test agent. As with the cell-free assays, agents which produce a statistically significant change in hedgehog activities (either inhibition or potentiation) can be identified" (col 51, lines 27-35). Marigo teaches that patched gene expression is responsive to Shh signaling. Marigo teaches that "[a]fter identifying certain test compounds as potential modulators of the target hedgehog receptor activity, the practitioner of the subject assay will continue to test the efficacy and specificity of the selected compound both in vitro and in vivo ... for subsequent in vivo testing ... agents identified in the subject assay can be formulated in pharmaceutical preparations for in vivo administration to an animal, preferably a human". Marigo further teaches that, "the present invention facilitates the development of assays which can be used to screen for drugs, including hedgehog homologs, which are either agonists or antagonists of the normal cellular function of the subject hedgehog polypeptides, or of their role in the pathogenesis of cellular differentiation and/or proliferation and disorders related thereto" (col 48, lines 40-46).

Marigo does not teach a method of screening using cultured lung cells that are not lung cancer cells. Marigo does not teach a method of screening that includes both determining whether the agent inhibits or attenuates hedgehog signaling and determining whether the agent inhibits cell proliferation or growth.

Bellusci teaches "a role for SHH in lung morphogenesis, and suggest that SHH normally regulates lung mesenchymal cell proliferation in vivo" (see Summary on pg 53). Bellusci teaches that "Shh overexpression results in an increase in epithelial and mesenchymal cell proliferation and to a lung which contains an abundance of mesenchyme and no functional alveoli" (pg 54). Bellusci teaches measurement of cell proliferation using BrdU incorporation, comparing the transgenic cells to normal cells as a control (pg 55; results shown in Table 1 on page 57). Bellusci further teaches that the "level of *Ptc* transcripts was clearly increased in the mesenchyme of the transgenic lung" (pg 58). Bellusci does not teach cultured lung cells.

Cardoso et al teaches cultured lung cells that are not lung cancer cells. On page 48, Cardoso teaches techniques for embryonic lung cell culture using lung explants

from rats sacrificed at gestational day 13.5. The cultured lungs exhibit "airway branching and differentiation of both epithelium and mesenchyme, reproducing the overall proximal-to-distal pattern seen in lung in vivo" (pg 49). Cardoso further teaches contacting the embryonic lung culture with a small organic molecule (retinoic acid) that increases hedgehog signaling (as opposed to the inhibition required by the instant methods).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to create transgenic mice that overexpress Shh as taught by Bellusci, prepare an embryonic lung cell culture from said mice using the technique taught by Cardoso, and to contact said lung cell culture with a test agent that is a small organic molecule as taught by Marigo, and to measure hedgehog signaling pathway (by measuring patched gene expression) as compared to a control as taught by Marigo (i.e., in the presence and absence of the test compound) and to further measure growth by BrdU incorporation as compared as taught by Bellusci as compared to a control (i.e., normal mice). Marigo provides motivation to identify hedgehog signaling antagonists that are also antagonists of cellular proliferation by teaching, "the present invention facilitates the development of assays which can be used to screen for drugs, including hedgehog homologs, which are either agonists or antagonists of the normal cellular function of the subject hedgehog polypeptides, or of their role in the pathogenesis of cellular differentiation and/or proliferation and disorders related thereto" (col 48, lines 40-46). The person of ordinary skill in the art would have been motivated to do so to identify a small organic molecule that is an antagonist (inhibitor) of hedgehog signaling and lung cell growth, as such can be used to inhibit hedgehog-dependent proliferation (as taught by Marigo).

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claim 1, 27 or 28, does not reasonably provide enablement for the method of claim 1, 27 or 28, wherein the agent disrupts the association of patched with smoothened. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention of claims 29-31 are methods to identify agents that inhibit or reduce the growth or proliferation of lung cells (including cancerous cells (claims 29 and 30) and non-cancerous cells (claim 31). The method steps include contacting said cells with an agent and determining as compared to a control, whether the agent inhibits (1) hedgehog/patched signal transduction and (2) cell proliferation. Claims 29-31 limit the agent to one that "disrupts the association of patched with smoothened".

No working examples are provided of agents that disrupt the association between patched and smoothened.

Stecca et al (2002; cited previously on the PTO-892 accompanying the 9/20/2005 Office Action) teaches that "[h]edgehogs are secreted glycoproteins that act through the transmembrane proteins Patched1 (Ptc1) and Smoothened (Smo) to activate an intricate signal-transduction pathway (Figure 1). Hh binds Ptc1, a protein with 12 transmembrane domains, and this releases the basal repression that Ptc1 exerts on Smo, a 7-transmembrane-domain protein that has homology to G-protein-coupled receptors" (pg 9). This is illustrated in Figure 1, which shows the Ptc1 protein exerting repression on Smo. In view of these teachings, the skilled artisan would predict

that disruption of the association between Ptc1 and Smo would relieve this repression and lead to an increase in hedgehog signaling, rather than an inhibition or attenuation as required by the instant claims.

Due to the large quantity of experimentation necessary to determine how to produce an agent that attenuates hedgehog signaling by disrupting the association of patched with smoothened, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 depends from claim 1 and recites "wherein the agent disrupts the association of patched with smoothened". It is unclear how this limitation relates to the agent used in the method of the parent claim. The method of parent claim 1 encompasses use of a broad genus of small organic molecule agents in screening, some of which are then identified as agents that inhibit hedgehog signaling and reduce cell proliferation. It is unclear how the characteristic recited in claim 29 limits the agents of claim 1. Does this characteristic limit the agents to be used in the method? That is, does it limit all of the agents to be screened to compounds already known to disrupt patched with smoothened? Or does it limit the identified agents only to those that then determined to disrupt patched with smoothened?

Claims 30 and 31 are rejected for the same reason as claim 29.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646